REMARKS

I. Amendments

Claims: Claims 17-25 are pending, claim 17 has been amended to clarify the claimed subject matter. The amendment does not constitute new matter and is supported throughout the specification and originally filed claims, more particularly at page 3, line 6; page 14, lines 23-25; and the Examples.

II. Claim Objections

The Examiner states that the term "LPR5" should be referenced in the independent claims first. However, none of the dependent claims appear to recite "LPR5" and it is therefore not clear to Applicant exactly what the objection is. Clarification is respectfully requested.

III. Rejections

A. Rejection under 35 U.S.C. § 101

Claims 17-19 and 24 stand rejected as the claimed invention allegedly is not supported by either a specific or substantial asserted utility or a well-established utility. Applicant respectfully traverses the rejection.

According to 35 U.S.C. § 101, "[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . . "

Under the Patent Office's Utility Requirement Guidelines:

> If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.
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> If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)). Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has either a well-established utility or is useful for a particular practical purpose. The present invention satisfies either standard.

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, any knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined. According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

> Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.
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> In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(http://www.genome.gov/pfv.cfm?pageid=10005834) (emphasis added). Thus, the knockout mouse has been accepted as one of the premier models for determining gene function, a utility that is specific, substantial and credible.

Commercial use and acceptance is one important indication that the utility of an invention has been recognized by one of skill in the art ("A patent system must be related to the

world of commerce rather than to the realm of philosophy." Brenner v Manson, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)). Commercial use of the knockout mice produced by Assignee Deltagen has been clearly established. Deltagen has created a database comprising characteristics derived from approximately 750 lines of knockout mice. Three of the largest pharmaceutical companies in the world, Merck, Pfizer and GSK, have subscribed to the database and requested access to the lines of mice for the purpose of studying gene function. In fact, all three institutions have ordered the presently claimed low density lipoprotein-related protein 5 (LPR5) knockout mouse. This commercial acceptance more than satisfies the practical utility requirement of section 101.

Applicant respectfully submits that this is not a case where the sole asserted utility is as an object of use-testing (See, Brenner v. Manson, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966); "We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product"). The dicta in Brenner related to the patentability of a chemical compound which itself had no known use. The Court opined that the utility could not solely consist of testing the compound in order to determine a utility for the compound itself. In contrast, the FPR-RS4 knockout mouse is useful for the study of the utility and function of the FPR-RS4 gene, and not for the purpose of establishing a utility for the mouse. The practical distinction is clear: one skilled in the art would not understand what to do with a compound without a defined use, but would immediately recognize the use of a knockout mouse having a specific gene disruption.

In the context of the issue of utility, knockout mice may be appropriately analogized to other research tools, with respect to which the Patent Office has commented:

> Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions

> that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function).

Applicant submits that since one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, a utility that is specific, substantial and credible, the invention has a well-established utility, thus satisfying the utility requirement of section 101. On this basis alone, withdrawal of the rejection with respect to the present invention is warranted, and respectfully requested.

In addition, the claimed invention is useful for a particular purpose. The Applicant has demonstrated and disclosed specific phenotypes of the presently claimed mice, i.e., retinal degeneration, increased anxiety and hypoactivity. Utility of a knockout mouse demonstrating any of these properties would be apparent to, and considered credible by, one of skill in the art.

The Examiner argues that although the specification suggests using the mice to test for neurological, neuropsychological or psychotic disease, the specification does not disclose one specific neurological, neuropsychological or psychotic disease linked to a disruption on LRP5. The Examiner argues that increased anxiety and significant hypoactivity are not specific to any disease, and that retinal degeneration has not been linked to the LRP5 gene in humans.

Applicant respectfully disagrees. The Examiner's arguments are similar to arguments made by the Patent Office with respect to pharmaceutical compounds the utility of which were based on murine model data, arguments which were dismissed by the Federal Circuit in In re Brana (34 U.S.P.Q.2d 1436)(Fed. Cir. 1995). The case involved compounds that were disclosed to be effective as anti-tumor agents and had demonstrated activity against murine lymphocytic leukemias implanted in mice. The court ruled that the PTO had improperly rejected, for lack of utility, claims for pharmaceutical compounds used in cancer treatment in humans, since neither the nature of invention nor evidence proferred by the PTO would cause one of ordinary skill in art to reasonably doubt the asserted utility.

The first basis for the Board's holding of lack of utility (the Board adopted the examiner's reasoning without any additional independent analysis) was that the specification failed to describe any specific disease against which the claimed compounds were useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. (In re Brana at 1439-40). The Federal Circuit reasoned that the leukemia cell lines were originally derived from lymphocytic leukemias in mice and therefore represented actual specific lymphocytic tumors. The court concluded that the mouse tumor models represented a specific disease against which the claimed compounds were alleged to be effective. (In re Brana at 1440).

The Board's second basis was that even if the specification did allege a specific use, the applicants failed to prove that the claimed compounds were useful.

The Federal Circuit responded: "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (Brana at 1441, *citing* In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)). From this it followed that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. (*Id.*)

The court held that the Patent Office had not met its burden. The references cited by the Board did not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, the references merely discussed the therapeutic predictive value of *in vivo* murine tests -- relevant only if the applicants were required to prove the ultimate value in humans of their asserted utility. The court did not find that the nature of the invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness. The purpose of treating cancer with chemical compounds did not suggest an inherently unbelievable undertaking or involve implausible scientific principles. (*Id.*)

The Court concluded that one skilled in the art would be without basis to reasonably doubt the asserted utility on its face. The PTO had not satisfied its initial burden. Accordingly, the applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. (*Id.*)

As in Brana, Applicant has asserted that the claimed invention is useful for a particular practical purpose, an assertion that would be considered credible by a person of ordinary skill in the art. For example, the LPR5 deficient mice have demonstrated retinal degeneration. Such mice are useful for studying whether retinal degeneration in humans is associated with mutations in the human LPR5 gene and for developing treatment strategies and therapeutics associated with any such mutations. That the specification does disclose a link between this particular phenotype and the gene in mice and humans does not detract from the utility of the mice. In Brana, the claimed compound had demonstrated activity against a murine tumor implanted in a mouse. Yet, the Federal Circuit found that utility had been demonstrated. Here, the invention relates to a disruption to a murine gene in a mouse. Like the tumor mouse model, the knockout mouse with a specific gene disrupted is a widely accepted model, the utility of which would be readily accepted in the art. It is submitted that one skilled in the art would be without basis to be reasonably doubt Applicant's asserted utility, and therefore the Examiner has not satisfied his initial burden.

Applicant has also determined that the presently claimed mice exhibit increased anxiety. Anxiety disorders are well-recognized conditions that are the subject of drug development studies and treatment strategies. For example, there are currently in excess of sixty (60) clinical trials enrolling patients for the study of anxiety disorders (http://clinicaltrials.gov/ct/screen/BrowseAny?path=%2Fbrowse%2Fby-condition%2Faz%2FA%2FD001008%2BAnxiety%2BDisorders&recruiting=true). This intense interest in studying treatments for anxiety disorders reasonably establishes that the phenotype and the disease/disorder are one and the same. Requiring the Applicant to establish a correlation between the phenotype and the disease/disorder is unnecessary and unwarranted.

Nonetheless, the claimed knockout mouse demonstrates that FPR-RS4 plays a role in anxiety disorders, correlating FPR-RS4 with a specific disorder. The utility of a knockout mouse demonstrating increased anxiety has been recognized as a useful tool in the discovery of anxiolytics. For example, Mombereau *et al.* (Neuropsychopharmacology (2004) 29, 1050-

62)(copy attached) discloses a $GABA_B$ receptor knockout having increased anxiety. Based on observations in the knockout mouse and subsequent pharmacological experiments using receptor antagonists, the authors proposed that the $GABA_B$ receptor serve as a novel therapeutic strategy for the development of anxiolytics.

The Examiner's own argument supports the predictiveness as well the utility of murine knockout models with respect to human gene expression deficiencies and mutations. The Examiner cites a LPR5 deficient mouse made since the filing of Applicant's application as demonstrating osteoporosis-pseudoglioma syndrome (OPPG), a condition that has also been associated with LPR5 gene mutations in humans. This supports a case for utility of the present invention as a correlation has been established between the LPR5 gene and OPPG in both mice and humans. That the Applicants have not yet performed this specific test for OPPG is irrelevant as it is likely an inherent property of Applicant's LPR5 knockout mouse.

It is respectfully submitted that the Examiner needs to assess utility in light of the nature of the invention. Applicant is claiming a knockout mouse. The burden should not be placed on Applicant to establish that LPR5 mutations in humans result in the same phenotypes observed in mice. This task is more appropriately placed on the commercial and academic entities conducting further research using the present invention. As cited by the Federal Circuit, usefulness in patent law necessarily includes the expectation of further research and development. (In re Brana at 1442).

In summary, Applicant submits that the claimed LPR5 knockout mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the LPR5 gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the specific phenotypes of the transgenic mice demonstrate that the mice are useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the arguments set forth above, Applicant does not believe that the Examiner has properly established a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant would be specific and substantial. (In re Brana; MPEP § 2107). Withdrawal of the rejections is therefore respectfully requested.

It is submitted that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 13-2725.

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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Date

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